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AIC-49

Published in Chemical and Engineering News 22: 588-593, (1944) under the title. "Penicillin--Science's Cinderella."

THE BACKGROUND OF PENICILLIN PRODUCTION[1]

By Robert D. Coghill, Fermentation Division
Northern Regional Research Laboratory,[2] Peoria, Illinois

Presented by Robert D. Coghill at the Annual Meeting of the
American Chemical Society at Cleveland, Ohio,
on April 5, 1944

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Introduction

Seldom within our memory has any topic so taken the interest of the scientific and lay world as has penicillin. For the past two years or more it has played Cinderella to the mycologists, chemists, and engineers of the whole English-speaking world. Product of the humble molds, which until comparatively recent years have been something to control rather than to cultivate, it has miraculously been clothed with the raiments of $20,000,000 worth of plants, is now attended upon by hundreds of footmen, and the party is proceeding with fanfare galore. Penicillin is very patently taking the limelight from its older sulfa sisters. Two years ago, those of us who were concerned with promoting the party used to wake up in the middle of the night and wonder whether, at the stroke of twelve, this lovely vision would flee, leaving us clutching at an empty glass slipper--the work and strife we had been through and the plants we had built. However, the stroke of twelve is now upon us, and we find the two stories are digressing; for the few dozens of spectacular cases upon which we had originally built our hopes have now been augmented by hundreds more like them, and whereas penicillin is not the cure-all which many may suppose it to be, its use in the treatment of bacteremias, osteomyelitis, pneumonia, gas gangrene, gonorrhea, and possibly syphilis has already saved hundreds of lives in what previously would have been hopeless cases, and the end is not in sight. Furthermore, we were not misled as to the innate character of our protege, for when properly prepared, penicillin is still found to be entirely non-toxic in the highest dosages needed for its most effective clinical use.

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[1] The expenses of the work described in this paper were met in part from Contract OEMcmr-100 with the Office of Scientific Research and Development, recommended by the Committee on Medical Research.

[2] This is one of four regional research laboratories operated by the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

In giving this paper, I hope to speak for all the hundreds of people who have made the penicillin development possible. From the early research workers to the operators in the currently producing plants, they have all given their utmost to the problem. This is true also of the government officials and company executives, who have carried the responsibility, shared in all of the headaches, and had none of the fun of immediate contact with the day to day progress of experimental work in the laboratory. In particular, I wish to speak for and pay tribute to my colleagues at the Northern Regional Research Laboratory, without whose collective efforts I would not be before you today. And while we are on the subject, I should at least mention one group who will never get any credit at all, the self-styled "penicillin widows." "They also serve who only sit and wait."

The production of antibiotic substances by micro-organisms is not an uncommon phenomenon. Pyocyanine was first discovered and clinically tested over 40 years ago, and since that time various micro-organisms have been shown to produce such protective substances. Until recently, gramicidin was the best known and most studied of these materials. Actually, however, when plating out soil samples, one frequently observes that a colony, which may be a mold, actinomycete, or bacterium, is inhibiting the growth of one or more colonies in its immediate neighborhood. It was just such a phenomenon as this which led to the discovery of penicillin by Dr. Alexander Fleming, Professor of Bacteriology at St. Mary's Hospital, London. In 1929, a spore of a mold, subsequently identified as Penicillium notatum, lodged in a Petri dish which harbored a culture of the pathogenic organism, Staphylococcus aureus. It soon became apparent to Professor Fleming that the mold colony was inhibiting the growth of the staphylococci, and he was quick to grasp the significance of this discovery. Fleming named the unknown material, which was responsible for the inhibition of the staphylococci, "penicillin", after the generic name of the organism which produced it. He continued to study this material from various other angles, and was the first to suggest that it might have value clinically if it were possible to produce it on a larger scale.

Professor Harold Raistrick, of the London School of Hygiene and Tropical Medicine, thereupon undertook the production of the material in some quantity. He studied media and cultural conditions, and got the first insight into the chemical nature of penicillin. However, his medical colleagues would not listen to his pleadings, and he could get no clinical tests made. Therefore, in view of penicillin's great chemical instability and extremely small yields (several p.p.m.) Raistrick, in 1932, published his work and turned to (then) more promising fields.

Penicillin thus very nearly died a natural death. It was not until seven years later that it was revived at Oxford University by a group of chemists and biologists under the leadership of Dr. H. W. Florey, Professor of Pathology. To this group, including Drs. Abraham, Chain, and Heatley, to my mind, goes a vast amount of credit for the penicillin development. They were the ones, who, under the greatest of difficulties imposed by reason of the war, prepared sufficient material to test clinically on a limited number of cases. Whereas these original tests left much to be desired, certain of their features were spectacular enough that it appeared urgent, for reasons connected with the war effort, to get sufficient material for more extensive clinical trials.

Because of the extensive bombing of England which was then current, the manpower shortage, and other contributing factors, England did not seem to be the place to attain the quickest results. Accordingly, the Rockefeller Foundation brought Drs. Florey and Heatley to this country to enlist help on the problem. They were immediately referred to the National Academy of Science and to Dr. Charles Thom, Principal Mycologist in the U. S. Department of Agriculture. Dr. Thom was instrumental in sending them at once to Peoria, where members of the staff of the Northern Regional Research Laboratory had had extensive experience in mold fermentations. They arrived on a hot day in July 1941, and sold us on the problem.

Professor Florey's continued efforts were not without effect in other quarters. Certain of our drug and chemical houses became interested enough to begin experimentation on production methods, and Dr. A. N. Richards, Chairman, Committee on Medical Research of the Office of Scientific Research and Development, put his shoulder to the wheel for the purpose of organizing efforts leading to the production of sufficient material for further clinical testing. Meetings were called of those commercial houses then known to be interested in the penicillin development (Merck, Squibb, Pfizer, and Lederle). The second of these meetings was held in December 1941. At this time, two difficulties were quite apparent. In the first place, the drug houses were obviously afraid to pool their information for fear of prosecution under the Sherman Anti-Trust Laws; and, secondly, the yields of penicillin were so low that it looked to be too stupendous a task to produce the kilo of crude penicillin which was thought to be the minimum amount needed for its proper clinical evaluation.

Fortunately, by that time we had made a very important discovery at the Northern Regional Research Laboratory. Dr. A. J. Moyer, Microbiologist in the Fermentation Division at that Laboratory, had found that the addition of corn steeping liquor to the medium upon which the mold grew increased the yields of penicillin by at least tenfold. This discovery, along with Dr. Moyer's efforts in strain selection, increased the yields of penicillin from 2 up to 40 Oxford units per cc. During this phase of the work we were greatly aided by the presence, for several months, of Dr. N. G. Heatley, of Oxford University, who made all of his knowledge available to us and trained our workers in the proper techniques involved in the cylinder-plate method of assay which he had devised in England.

In my estimation, the Northern Laboratory's discovery of the action of steep liquor was possibly the greatest single factor in making the commercial production of penicillin feasible. An extension of this work has resulted, in our laboratories, in a hundredfold increase in the yields of penicillin surface cultures, i.e., from 2 to 200 Oxford units per cc. in small Erlenmeyer flasks. Yields in larger containers are generally lower, but current commercial runs now occasionally exceed 100 units per cc. When one considers that a yield of 100 units per cc. represents only 0.06 mg. of pure penicillin per cc., half of which is lost during recovery operations, it is obvious why the 2-unit yield we started with looked rather discouraging.

The work in Peoria has been supported largely by the U. S. Department of Agriculture, but with the Committee on Medical Research of the Office of Scientific Research and Development making substantial contributions for equipment and technical assistants. Originally begun in an attempt to increase yields and investigate the feasibility of producing penicillin in submerged culture, it has been expanded to include studies of recovery methods, purification, chemistry, and an intensive search for new organisms. (The numerous reports on this work have been classified as "Restricted" and can be obtained only from Dr. Richards, Chairman, Committee on Medical Research.)

As yields increased and more penicillin was produced, clinical data began to accumulate, and it soon became apparent that penicillin was something to conjure with.

Five commercial houses were largely responsible for producing and making available the penicillin which was used in establishing its place in the clinical picture. These firms, Merck, Squibb, Pfizer, Abbott, and Winthrop, cannot receive too much credit for their pioneering efforts, for it was the money which they gambled, in some cases exceedingly large amounts, which clinched the value of the product and paved the way for the more recent entries into the manufacturing field. The three first-named of these companies turned their whole penicillin production over to the Committee on Medical Research for its clinical research program--at first for nothing, later at less than cost, finally, when the amounts had become large, at commercial prices.

The clinical testing program of the Committee on Medical Research was organized under Dr. Chester Keefer, of the Evans Memorial Hospital, Boston, Massachusetts. It is he who has had the hardest job of all--that of deciding who should get penicillin and who would be denied, while at the same time having to keep in mind that a well rounded, comprehensive picture of its effectiveness had to be obtained, particularly with reference to its place in military medicine. Since he controlled practically the whole supply of penicillin, all applications had to pass through his hands--and for that matter still do, as far as civilians are concerned. It was necessary to see that the small available supplies of penicillin were not wasted on types of cases where it was known to be ineffective. All this he did impartially and fairly, and thus the Committee on Medical Research was able to get a maximum of information with the least expenditure of the precious material, a result which could not have been obtained had the work been done independently in a number of centers.

By July 1943, the combined efforts of the original pioneering companies and the clinicians had well established the value of penicillin, and much unfortunate newspaper publicity had served to whet the public appetite. Literally scores of potential producers wanted to get on the band wagon. In fact, the movement assumed the characteristics of an autocatalytic reaction. Many of these potential producers had been quietly carrying on research on production methods and knew what they were about. These were welcomed into the field (at least on the part of the Government), as it was obvious that prodigious amounts of penicillin would be needed for the Army, Navy, and civilian populations. But there were many others--ranging from the obviously competent all the way down to the farmer in Louisiana who wrote that down there the soil, temperature, and humidity were just right for growing the mold; the prospector from Arizona who sent us a beautiful lichen-covered rock and offered to send any amount more; and the inventor from a midwestern state, one step of whose process was to be carried out by men wearing rubber gloves, rubber boots, and shorts!

Assay Methods

When dealing with a substance of unknown nature, present in unknown amounts, and grossly contaminated with a variety of impurities, one is forced to adopt some arbitrary unit of measurement. This was done very early by Drs. Florey and Heatley, and became known, first as the Florey unit, and later, at Professor Florey's request, as the Oxford unit. From the assayer's point of view, this was a very convenient unit, based as it was, on the size of a zone of inhibition observed under stipulated conditions. Unfortunately, from the producer's point of view, it is aggravatingly small, representing only 0.6 micrograms of penicillin. This is, of course, a reflection of the exceedingly high bacteriostatic power of penicillin, which will inhibit the growth of certain gram positive organisms in dilutions of more than one to a hundred million, although it is not particularly effective against gram negatives.

Several methods are now in use for penicillin assay. Probably the most widely used, and the one practiced at Peoria, is known as the cylinder-plate method.

After a base nutrient agar has hardened in the bottom of a Petri dish, it is inoculated with a warm agar suspension of the test organism, generally a culture of Staphylococcus aureus. Within a few minutes, this agar, too, has hardened and five small cylinders are then dropped lightly on the surface, where they form a water-tight seal. Dilutions of the unknown penicillins are then pipetted into some of the cylinders, while a known standard solution is placed into one or more of the others. The plate is placed in the incubator promptly, and two processes begin to take place. The penicillin begins to diffuse outward from the bottom of the cylinder into the agar. Meanwhile the bacteria begin to grow. In 4 to 7 hours a point is reached where the inhibition zones become obvious. The plates are read at 16 hours. The square of the diameter of the zone of inhibition is proportional to the log of the concentration of the penicillin. As certain variables in the technique change, so does the standard curve, but with a trained crew carrying on the same way day after day, the errors so incurred are comparatively small. This cylinder-plate method has several advantages. One does not have to use sterile technique, more assays per man-hour can be obtained, and there is no interference from Penicillin B or Notatin, another powerful antibiotic produced by the same mold.

Assays can also be carried out by the dilution method in broth tubes, but sterile technique must be used, which is a great bother. In this method, inhibition of growth can be measured turbidimetrically, or one can determine the point at which inhibition ceases. In any assay method, one point cannot be overemphasized. It is imperative to keep very close to a standard penicillin. This "standard" has been the chief source of assay trouble, a plague from which everyone has suffered intermittently. Standards have tended to be unstable, and with the lack of a generally recognized and stable standard, it is easy to visualize the difficulties which all have had. We have tried to keep as close as possible to the original Oxford unit--but if we have inadvertently drifted away from it slightly, there is no real harm done. The Food and Drug Administration has now set up a new standard, consisting of three grams of pure crystalline penicillin, which has been demonstrated to be stable if properly stored. This is our National Standard, and, the English willing, can become an International Standard. Its value has been established at 1,650 units per milligram, which we believe to be reasonably close to the original Oxford unit.

Production Methods

There are three main methods of producing penicillin, all of which are or will shortly be in commercial operation. These will be taken up in turn, and can conveniently be referred to as the surface culture, submerged culture, and bran culture methods. A few words, first, about the organisms used.

A. Organisms Used

Penicillin production is not confined to one species of mold, although Penicillium notatum is the organism most commonly associated with it. Actually, P. notatum is a member of a large aggregate of forms commonly designated as the P. chrysogenum group. When large numbers of cultures are examined, it is found that there exists a continuous graded series of strains ranging from typical P. notatum to typical P. chrysogenum. Of our several best penicillin producers, one is a P. chrysogenum; the rest can more properly be called P. notatum. In addition to this series of organisms, Aspergillus flavus, a member of an entirely different genus, produces penicillin or something very closely akin to it, but in smaller amounts.

P. notatum NRRL 1249.B21 is the strain generally used by industry for the production of penicillin in surface culture. It is a better producing monospore isolation from a strain of P. notatum obtained from Dr. George Harrop of the Squibb Institute for Medical Research, and stems directly from Professor Fleming's original strain.

NRRL 832 is the strain of P. notatum which is generally used for production of penicillin in submerged or deep fermentations. This organism is not descended from that of Fleming, but was one of those found in the culture collection of the Northern Regional Research Laboratory. Microbiologists familiar with these two strains can readily distinguish between them, although they are members of the same species. Both of these organisms may be obtained from the American Type Culture Collection.

During the past nine months, Dr. K. B. Raper of our Peoria laboratory has isolated over 200 new strains of molds belonging to the notatum-chrysogenum group in an effort to find better penicillin-producing strains. This program has not been without results, at least two superior strains having been obtained. When one considers the cost of the plants engaged in penicillin production, and the tremendous value, both monetary and humanitarian, of the product produced, a million dollars would not be too much to spend at this time to get an organism which would increase production by as much as 50 percent. The Office of Production Research and Development has an extensive supplementary program in progress at various schools in an effort to attain this goal.

B. Production in Surface Culture

This is the old standard method of conducting mold fermentations, and the one by which all of our early penicillin was produced. It consists in seeding spores of the mold on the surface of a culture medium and working with the heavy pellicle or mat of mold mycelium which forms. When many exploratory experiments are necessary, a convenient method is to use 50 cc. of medium in a 200 cc. Erlenmeyer flask. If production is wanted, one can operate in milk bottles, 3-liter Fernbach flasks, or even in large pans.

Various factors affect the yields of penicillin obtained in surface cultures in such a way that one almost invariably obtains much larger yields in the small containers than is possible in larger equipment. This is due, in part, to the fact that the depth of medium in small flasks is generally much less (1 to 2 cm.), resulting in better diffusion of the nutrients to the mycelium. There also tends to be more evaporation, which affects the yields when they are expressed in units per cc. From the commercial point of view, of course, the yield per container is more important than the units per cc., and actually the depth of medium is increased to 3 to 4 cm. Above this, yields per container go down, due to insufficient diffusion, and, furthermore, recovery costs go up due to the larger volume of liquor which has to be handled.

On the proper culture medium, which cannot be described here, yields of 200 Oxford units per cc. can be obtained in small Erlenmeyer flasks in 6 to 7 days. The process, as commercially practiced in bottles or pans, yields 50 to 100 units per cc. in 7 to 11 days. This method has several advantages over the other procedures to be described later. Yields are higher and, on the whole, simpler equipment can be used. The big advantage, however, is its safety. Conducted as it is, in many small units, contamination of the fermentation, if it occurs, does not destroy a whole run. It should be mentioned here that many common contaminating organisms, such as species of Pseudomonas, Bacillus subtilis, and even certain strains of Escherichia coli, produce enzymes which very quickly destroy all the penicillin present. It is therefore obligatory that absolutely all contaminants be rigorously excluded.

The most serious objection to the surface culture method of producing penicillin is its very high labor cost. To process 10,000 gallons of medium requires as many as 100,000 to 125,000 bottles, which is several days' run in even the largest of the bottle plants.

C. Production in Submerged Culture

The method of conducting mold fermentations in large vats, where the mycelium grows in a submerged condition, had been extensively studied in the U. S. Department of Agriculture before my connection with the Department. This is undoubtedly the best method of conducting mold fermentations, when it will work. (The citric acid fermentation, for instance, will not work under these conditions.) Accordingly, work was done very early, in order to determine whether the mold would produce penicillin when grown under the surface of the culture medium. Greatly to our satisfaction, it was found that this was indeed the case. It thus became possible to think in terms of large vat fermenters, where labor costs could be cut enormously.

In order to achieve a surface growth of mold, it is necessary to aerate and agitate the culture in some manner, in order to prevent the surface growth which the organism prefers. This can be done in a variety of ways, either by culturing in vats equipped with aerators and agitators, in rotary drum fermenters (such as those in use in the Peoria laboratory), or in shaken flasks. For laboratory purposes, where one wishes to perform many experiments of an exploratory nature, the shaken flask is the most convenient, although the results so obtained cannot always be extrapolated to other equipment. In place of the heavy pellicle seen in the surface cultures, the mold in shaken cultures grows as small pellets, having somewhat the appearance of tapioca. The size of the pellets varies inversely with the amount of inoculum used. In vat or rotary drum fermenters, where agitation has been quite vigorous, the growth may, however, tend to become quite filamentous in nature.

The Fleming strain of P. notatum does not give good results under submerged conditions, another organism, NRRL 832, having to be used. In small shaken flasks, yields of 50 to 100 Oxford units per cc. can be realized in 4 to 5 days. In vat cultures, we can obtain yields of 40 units per cc. in 2 days, and as high as 80 units per cc. on occasion.

As indicated earlier, the big advantage of the submerged method of operation is the saving in labor. However, the operation of large vat fermenters under absolutely aseptic conditions is beset with many difficulties, and the history of the development of the submerged production of penicillin has been a succession of heartaches and disappointments for those concerned. Periods of success have been followed by inexplicable failures. As one source of difficulty after another was eliminated, failures became less frequent and this process is now operating with reasonable success. The real reason for all of this trouble is that the conditions under which the fermentation is run are ideal for the development of contamination. The excellent nutrient qualities of the medium, its essentially neutral pH, as well as the necessary aeration, all make for the quick growth of any stray organisms which might enter at one place or another. Combine this with the fact that a little contamination at the end of the run will completely eliminate the penicillin in a very short time, and you can begin to understand why this fermentation is so difficult to run as compared with what had previously been considered a ticklish problem itself, the butyl alcohol-acetone fermentation, where a little contamination at the end of the run merely lowers the yield slightly. Add to this the necessity of delivering to the fermenters very large volumes of absolutely sterile air, and one can begin to appreciate why the production of penicillin in vat fermenters has required the development of a technique in the elimination of contaminants above and beyond anything which had heretofore been necessary or practicable in industry. The difficulty of attaining this goal can be properly appreciated only by those who have attempted to achieve it. The "know-how" of this technique has finally been acquired so that it is probable that the majority of runs are now successful, at least in the hands of those with a year or two of experience behind them.

D. Production of Penicillin on Bran

Before leaving the subject of penicillin production, mention should be made of a third *modus operandi*, which holds promise but is also beset with its own variety of difficulties. This method consists in growing the mold on moist bran. The bran may be spread thinly in trays or processed in a rotary drum. It is first sterilized and then inoculated with a culture of *P. notatum*. After growth has taken place for 2 to 4 days, the substrate may contain as much as 200 to 400 units of penicillin per gram of dry bran. It is then placed in percolators and the penicillin extracted by a suitable solvent. The penicillin is thereafter recovered as in the case of the other methods of production.

This process for producing penicillin has several difficulties, two of which will be mentioned. Both of them are a direct result of a very characteristic property of bran; namely, it is a very poor heat conductor. One result of this is that it has been found very difficult to effectively sterilize the bran before inoculation, with resulting large losses due to contamination. The second difficulty also has to do with heat transfer. As is "well known to those skilled in the art," penicillin production occurs best at a temperature of 24° C. There is, however, a good deal of heat produced during the fermentation which has to be dissipated in some manner. This is easily taken care of in the surface and submerged plants by air conditioning and cooling coils, and I have no doubt the problem will also be solved by the advocates of bran as a substrate.

In favor of the bran process, one can say that relatively large amounts of penicillin can be produced with the expenditure of materially less labor than is necessary in a bottle plant.

E. Recovery Methods

Just as in the fermentation phase of the process, so in the recovery of the penicillin in a form suitable for clinical use, a number of difficult situations have to be met. After removal of the mold mycelium (or bran) by filtration or centrifugation, one has a clear, yellow to brown, solution which still contains sufficient nutrients that contaminants, if given half a chance, can very quickly destroy all of the penicillin. The broth must therefore be protected either by chilling, by the addition of a disinfectant, or by aseptic handling. Furthermore, there is actually very little penicillin there. The usual content of 30 to 100 units per cc. is equivalent, roughly, to between two and six thousandths of one percent of penicillin. Add to this infinitesimal concentration its great instability to acid, alkali, heavy metals, and certain other reagents which we might like to use, and one can appreciate why the recovery of penicillin is very much like looking for a very unstable needle in a haystack!

Secrecy orders do not permit our going very far into actual operating methods. Before the ban, however, a certain amount was published by the English, which it does no harm to repeat. Penicillin, as used clinically, is the sodium salt of a strong organic acid. Current recovery procedures are variants of that originally published by the Oxford University group, in which the pH of the broth is set between 2.0 and 3.0 and all of the free organic acids are extracted into a solvent such as ether, chloroform or amyl acetate. At this point there are two difficulties. In the first place, penicillin is extremely unstable at this pH, as indicated by data accumulated at the Northern Regional Research Laboratory. Due to this high instability against acid, it is obvious that the extraction step should be carried out at as low a temperature as possible, and in as short a time. The solvent solution of the free penicillin is then shaken out with aqueous sodium bicarbonate to yield a solution of the sodium salt, or, if greater purity is desired, it can be shuttled back and forth between various solvents and buffer solutions of appropriate pH, ending up finally as the sodium salt.

The final solution of sodium penicillin has to be packaged bone-dry, due to the fundamental instability of penicillin in aqueous solution. If this drying operation is carried out at ordinary temperatures, very extensive decomposition takes place. Therefore, penicillin has to be frozen and dried from that state, in the same fashion that all of our dried plasma is produced. The freeze-drying operation may be carried out either in bulk or in the final ampoule. This has resulted in a demand for a vast amount of difficultly procurable equipment.

As finally obtained, penicillin is a powder ranging from pale yellow to dark brown and generally containing 100 to 500 units per milligram. It represents a mixture of the sodium salts of most of the organic acids contained in the original broth, and includes about 8 to 30 percent of sodium penicillin. It is rigorously tested for potency, sterility, toxicity, and pyrogens, all of which is under the control of the Food and Drug Administration.

Purification and Chemistry

Naturally, such a biologically powerful molecule as penicillin challenges the organic chemist, and many of us devoted attention very early in the development to its purification and isolation. Due to the instability of the material, however, chromatographic methods were the only ones which were practicable. After much labor in many laboratories, Drs. McPhillamy and Wintersteiner of the Squibb Institute for Medical Research were the first to isolate the pure crystalline material. The proof of structure and synthesis of penicillin is very properly the goal towards which we aim. However, its chemistry is deemed of sufficient importance to be a military secret and nothing can be said of it. One answer, however, can be given to the periodically recurring rumors of penicillin synthesis, "We are not thinking of scrapping our fermentation plants yet."

The Penicillin Production Program

The first two years of work on penicillin was a period of research and of slowly expanding production, during which time we tried to get the answer to the fundamental questions, "Is penicillin good enough to justify the great production difficulties? If so, how much will the armed forces need, and how can we improve existing production methods?" By May of 1943, we knew the answer to the first question was "yes," and we had tentative answers to the second and third. Penicillin then became a production problem, and the responsibility for making it available was taken over by the War Production Board. Mr. Fred J. Stock, Chief, Drugs and Cosmetics Section, Chemicals Bureau, and his assistants accordingly proceeded to consider applications for the erection of penicillin plants and to issue the necessary priorities. By September 1943, the situation had become so demanding that it was found necessary to appoint a penicillin Coordinator, Dr. A. L. Elder. At this time, also, the War Production Board's subsidiary, the Office of Production Research and Development, came into the picture, and with the assistance of Dr. L. A. Monroe established supplementary projects at the University of Wisconsin to study fermentation, and at Pennsylvania State College to improve recovery methods.

The War Production Board had many difficult decisions to make. How many plants should be erected? What should be the proportion of the production allocated to each of the three possible processes? They knew that they could count absolutely on the bottle plants coming through to produce as much penicillin as they cared to allot to that method, but how much should they gamble on the continued successful operation of the submerged plants? Moreover, should they allow the operators of the latter to use 10,000-gallon tanks, which they had never tried to operate, or make them stick to 1,000-gallon tanks, which they knew they could manage, but which would entail the manufacture of ten times as many motors, agitators, tanks, and valves? These are just samples of the problems which the War Production Board had to meet. How successful Mr. Stock, Dr. Elder, and their staff were in their solution can be judged by the following table, which shows how penicillin production has progressed.

Table I.- Penicillin Production

		Millions of Units
1943	January to May, inclusive	400
	June	425
	July	762
	August	906
	September	1,787
	October	2,872
	November	4,846
	December	9,194
1944	January	12,550
	February	18,700
	March (estimated)	40,000

I think that you will all agree with me that the War Production Board and the firms in question have accomplished an exceedingly fine piece of work.

To attain this volume of production, 21 plants are being erected in this country and Canada, at a total cost of nearly $20,000,000. By far the major part of the financing has been done with private capital.

Where does all of this penicillin go? In July 1943, the War Production Board placed a freeze order on all penicillin production. Each month, expected production was allocated to various agencies. The armed forces are taking nearly all of the supply. It is felt that, with near term production of penicillin expected to increase still more, there will be sufficient available to treat all urgent civilian cases in the relatively near future.

And what of the cost? The first price quoted for penicillin, and acknowledged to be less than cost, was $20 per 100,000 units. The last price quoted has been $3.25 for 100,000 units, an 84 percent reduction in a year. It is approximately correct to say that, on the average, a severe case requiring penicillin therapy will need about a million units, except for gonorrhea, which requires only 100,000 to 150,000 units. At $3.25 per 100,000 units, a severe septicemia could be treated for $35, or gonorrhea for less than $5.00. However, the price will undoubtedly go much lower, and penicillin will be within the reach of everybody.

It is interesting to calculate the weight of penicillin to be produced. Based on a tentative production program of 200 billion units per month, and on the potency assigned to the National Standard, 1,650 units per milligram, these $20,000,000 worth of plants will produce approximately 9 pounds of pure penicillin per day. This seems utterly fantastic! And yet this amount will treat approximately 250,000 serious cases per month. For our fighting men it will mean the saving of thousands of lives, to say nothing of arms and legs.

In closing, allow me to apologize for having left untouched many of the aspects of the picture about which most of you might have wished to hear. Wartime restrictions prevent the discussion of many of the most interesting phases of the subject, such as chemistry. This will all come to light in due course, the background which I have pictured at least having served to introduce you to the subject. The whole penicillin development has been a monumental undertaking. Its success has been due to the persistence and determination of government and industrial research workers, the vision and drive of our pharmaceutical and chemical manufacturers, and the whole-hearted backing of the Army, Navy, and War Production Board. We at the Northern Regional Research Laboratory are very conscious of the privilege it has been to play our part in what may well turn out to be one of the outstanding developments of the war.